REMARKS

Claims 7-32 were pending in this application. Claims 30-32 have been withdrawn from consideration by the Office pursuant to an Election of Species requirement. Examined claims 7-30 were variously rejected under 35 U.S.C. § 112.

Claim 7 has been amended herein to indicate the claimed polynucleotide encodes a detoxified LT polypeptide that is (i) at least 8 amino acids in length and (ii) includes Ala-72 and in which (iii) Ala-72 is substituted with an arginine residue. Withdrawn claims 30-32 have been similarly amended to with regard to SEQ ID NOs:2-4. Claim 26 has been amended to depend from claim 20 rather than claim 19. Thus, claims 7-32 are pending as shown above.

The amendments are made solely to advance prosecution and are not intended as an admission that the Examiner's position was correct. No new matter has been added as a result of these amendments and entry thereof is respectfully requested.

ELECTION OF SPECIES

Applicants reiterate that their traversal of the election of species requirement was based on the fact that it would not be unduly burdensome to search all sequences together. In addition, Applicants noted that the Office had not properly delineated the differences between the allegedly distinct species encompassed by these claims and, accordingly, Applicants could not elect a single species. In any event, it is to be understood that upon allowance of a generic claim, Applicants will be entitled to consideration of claims to the additional species.

DRAWINGS

FIG. 12 is again objected to as allegedly introducing new matter. (Office Action, paragraph 3). The new matter rejection is based on three arguments. First, it is maintained that Domenighini (the source of FIG. 12) is not incorporated by reference into the disclosure. Second, it is alleged that the drawings includes "essential material" that may never be incorporated by reference to a non-patent publication. Third, it is maintained that "there is nothing in the specification as filed suggesting LT-A sequences having residues other than Ala at position 72, whereas SEQ ID NOs:3 and 4 on the figure present proteins with different residues (I and L) therein." *Id.*

Applicants address each issue in turn.

Incorporation by Reference of Domenighini

With regard to incorporation by reference of Domenighini et al., Applicants remind the Office that the proper legal standard for determining if a reference is "properly" cited is not

determining whether the words "incorporation by reference" appear next to the reference. Rather, the proper test involves examining the application for the context in which the reference is cited. *See, e.g.,* MPEP 608.01(p) and *In re Hawkins,* 179 USPQ 157 (CCPA 1973). Thus, mere reference, for example by listing of a number of references without pointing to specific teachings in these references or by simply using the words "continuation in part," is not considered to be "proper" incorporation of these references. See, *In re de Seversky*, 177 USPQ 144 (CCPA 1973). In contrast, citing a reference for specific teachings in a specific context is not a "mere" reference. Indeed, the Federal Circuit has held that simply mentioning the *title* of a journal article can be sufficient to describe claims, in view of the understanding of the skilled artisan. *Atmel Corp. v. Information Storage Devices Inc.,* 53 USPQ2d 1225, 1231 (Fed. Cir. 1999).

In the case at hand, Applicants (on page 5, lines 25 to 31,emphasis added) properly cited Domenighini in the specification as filed for what this reference teaches about LT-A sequences:

> It will be appreciated that in derivatives of LT-A, such as fragments, or in LT-A proteins of different *E. coli* strains, **the amino acid residue to be mutated is that which corresponds to Ala-72 as defined for LT-A in Domenighini *et al.* [*Molec. Microbiol.* (1995) 15:1165-1167]**. Ala-72 is located on the second turn of the alpha-helix in LT-A and faces the NAD binding site.

Clearly, the reference to Domenighini in the instant disclosure relates to the specific teachings it provides regarding LT-A sequences and for alignment of these various sequences showing the position of amino acids relative to the wild-type Ala-72 in the porcine LT-A protein. Accordingly, given the context and manner in which the Domenighini is cited in the application as filed, it is plain that this reference is properly incorporated by reference for everything it teaches about LT-A sequences. As such, the position that Domenighini is not "properly incorporated by reference" is unsustainable and Applicants are entitled to amend their specification to include any material incorporated from Domenighini, including FIG. 12 (corresponding to FIG. 1 of the reference).

"Essential Material"

The Office Action also errs in stating that "essential material may not be incorporated by reference to non-patent publications." (Office Action, paragraph 3).

In fact, it is axiomatic that an applicant must be afforded an opportunity to incorporate material deemed essential into their specification, regardless of the source of the material. Thus, material deemed "essential" from a non-patent publication can be incorporated into the disclosure. *See, e.g.,* M.P.E.P. 608.01(p) (emphasis added):

> The incorporation of essential material in the specification by reference to a foreign application or patent, **or to a publication** is improper. **Applicant is required to amend the disclosure to include the material incorporated by reference**. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Indeed, in *Hawkins,* the CCPA made clear that subsequent amendment of the specification to recite the teachings of the reference will properly cure any defect in disclosure alleged by the Office and that editing the application by inserting that which was previously properly referenced does not raise new matter issues. *In re Hawkins,* 179 USPQ at 161.

In the pending case, Applicants have entirely cured the alleged omission of essential material by inserting the sequences of Domenighini into the specification. Thus, the material deemed "essential" has been properly incorporated into the disclosure by the addition of FIG. 12.

Furthermore, the undersigned practitioner again declares that the amendatory material (FIG. 12) consists of the same material as found in FIG. 1 of Domenighini et al., cited on page 5, lines 25-31 of the specification as filed.

Simply put, the material deemed essential by the Office has been properly incorporated as FIG. 12 and, as such, any defect in the disclosure as been cured without raising any new matter issues.

LT-A Sequences Having Residues Other than Ala at position 72

Finally, Applicants strongly disagree with the assertion that the specification as filed fails to teach LT-A sequences having residues other than Ala at position 72. In fact, in the passage reproduced above from page 5 of the specification makes it abundantly clear that residues other than alanine-72 were explicitly contemplated and disclosed (emphasis added):

> It will be appreciated that in derivatives of LT-A, such as fragments, or in LT-A proteins of different *E. coli* strains, **the amino acid residue to be mutated is that which corresponds to Ala-72 as defined for LT-A in Domenighini *et al.* [*Molec. Microbiol.* (1995) 15:1165-1167]. Ala-72 is located on the second turn of the alpha-helix in LT-A and faces the NAD binding site.**

FIG. 12 (corresponding to FIG. 1 "correct" of Domenighini) makes clear that the residue may be different and, moreover, that the residue corresponding to Ala-72 may be numbered differently. In the text describing the drawings, both Domenighini and Applicants make it plain that "dashes show residues identical to the upper most sequence" while gaps (introduced to maximize alignments) are shown by periods. Therefore, it would be readily apparent to the skilled artisan that the residue "corresponding" to Ala-72 refers to the residue on the second turn of the alpha-helix facing the NAD binding site, regardless of its number in the polypeptide or the particular residue at that position. For instance, in the case of SEQ ID NO:3 the residue corresponding to Ala-72 is Ile-70 while in the case of SEQ ID NO:4, the residue corresponding to Ala-72 is Leu-70. Thus, the specification as filed clearly teaches LT-A sequences having residues other than Ala at the position corresponding to residue 72 of SEQ ID NO:1.

In sum, Applicants submit that FIG. 12 does add any new matter. Nonetheless, if the Examiner prefers, Applicants would be willing to incorporate the sequence directly into the specification following the reference to Domenighini.

35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 7-30 were rejected for a variety of reasons under 35 U.S.C. § 112, first paragraph as allegedly not described by the specification as filed. (Office Action, paragraphs 4-6). In particular, specific octapeptides recited in previously pending claims 7-30 were alleged to not be described in the specification as filed. (Office Action, paragraphs 4 and 5). In paragraph 6, it was alleged that the specification does not describe polynucleotides encoding fragments of full-length LT-A.

To the extent that the foregoing amendments have not obviated the rejections, Applicants traverse.

With regard to the rejections set forth in paragraphs 4 and 5 of the Office Action, Applicants submit that the specification as filed clearly describes any octapeptide fragment including the Arg substitution at the residue corresponding to Ala-72. Nonetheless, in a sincere effort to advance prosecution, the octapeptide recitations have been removed from the claims, thereby obviating these rejections.

Applicants further submit that the assertion made in paragraph 6 of the Office Action that the specification as filed does not address polynucleotides encoding fragments of LT-A is in error. In fact, on page 7, lines 19-21, Applicants have explicitly indicated that one aspect of the invention is a DNA sequence encoding an immunogenic detoxified protein according to the first aspect of the invention. The "first aspect" referred to in this passage clearly and unambiguously includes within

its scope immunogenic, detoxified fragments of LT-A, as described for example on page 3 line 37 to page 4, lines 2-3 (emphasis added):

> Accordingly to a first aspect of the present invention, there is provided an immunogenic detoxified protein comprising the amino acid sequence of subunit A of an *E. coli* heat labile toxin (LT-A), **or a fragment thereof**, wherein at least amino acid Ala-72 in said sequence **or fragment** is mutated.

Thus, the specification as filed conveys to the skilled artisan that Applicants were in possession of the claimed subject matter. Accordingly, withdrawal of this rejection is in order.

35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT

Claims 7-30 were also rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification as filed. (Office Action, paragraph 7). Although it is acknowledged that the application as filed demonstrates that full length LT-A has reduced toxicity as compared to wild type, it is maintained that the specification does not enable the use of octamers previously recited in the claims. *Id.* It is alleged that there is no guidance on what fragments are required to maintain immunogenicity of the fragments required by the claims and that there are not sufficient structural characteristics for DNA encoding these fragments. *Id.*

To the extent that the foregoing amendments do not obviate this rejection, Applicants traverse.

The test of enablement is whether one of skill in the art could make and use the invention based on the specification as a whole. A specification must be taken as enabling in the absence of evidence to the contrary. The courts have consistently held that not every last detail of any invention need be described, "else patent specifications would turn into production specifications, which they were never intended to be." See, e.g., *In re Gay*, 309 F.2d 769, 774 135 USPQ 311, 316 (CCPA 1962) and *Staehelin v. Secher* 24 USPQ2d 1513, 1516 (BPAI 1992). Thus, the proper legal standard for determining enablement is whether the specification provides enough guidance as to the existence of methods and materials that allow one of skill in the art to practice the claimed invention without undue experimentation. (see, *e.g., In re Wands,* 8 USPQ2d at 1404, citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976)).

The record is replete with evidence establishing that it would require, at the very most, routine experimentation for a skilled artisan to identify binding DNA sequences encoding the claimed fragments. In particular, the specification teaches how to design expression vectors that include DNA sequences encoding the claimed fragments. *See, e.g.,* pages 19-42. In addition, the

specification clearly teaches how to test any fragment for both immunogenic and toxicity characteristics. *See,* Examples.

In other words, using standard molecular biological and immunological techniques well known to those working in the field, it would require only routine experimentation for a skilled artisan to follow the teachings of the specification and determine whether any DNA sequence encoding a fragment of LT-A as claimed was immunogenic and detoxified. Thus, the specification as filed more than amply satisfies the enablement requirement of Section 112, as one of skill in the art could make and use the claimed molecules without undue experimentation following the guidance set forth in the specification as filed.

Furthermore, the courts have emphatically rejected the notion that one of ordinary skill in the art must have reasonable assurance of obtaining positive results in all cases. *See, In re Angstadt,* 190 USPQ 214, 219 (CCPA 1976). So long as it is clear that some species render a method operative, the inclusion of some possible inoperative species does not invalidate the claim under paragraph 1 of 35 U.S.C. §112. *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988. Moreover, even evidence of the need for some experimentation does not invalidate a claim on ground of undue experimentation, nor does it fulfill the PTO's burden of proof. (*In re Angstadt* at 218; *In re Morehouse*, 545 F.2d 162, 165, 192 USPQ 29, 32, CCPA 1976.)

Thus, in the pending case, Applicants are in no way required to show that all fragments of the LT-R72 mutant are immunogenic and/or detoxified. All that is required is that the specification teaches a skilled practitioner how to, without requiring undue experimentation, select a polypeptide including at least 8 residues and the Ala-Arg mutation, make a DNA sequence encoding this polypeptide and test the polypeptide encoded by the sequence to determine if it is immunogenic and detoxified.

For the reasons of record and those reiterated above, the specification more than satisfies this requirement. The techniques needed to practice the claimed invention would be routine to the skilled artisan in light of the teachings of the specification. If, using the procedures set forth in the specification, the polypeptide encoded by the selected DNA sequence is not detoxified or is not immunogenic, it does not fall within the scope of the pending claims.

Still further evidence regarding enablement is submitted herewith. In particular, Applicants also direct the Examiner's attention to Stylos et al. (1977) *Clin Exp Immunology* 27(2):245-253 and Habeeb et al. (1976) *J Biol Chem* 251(15); 4616-4621. These references indicate that fragmentation analysis of antigen proteins was routine experimental procedure at the date of filing. Fragmentation can be followed by analysis of resultant fragments to confirm that adjuvanticity has been retained.

As described in Stylos and early as 1976, fragmentation of antigenic peptides was used to isolate fragments that possessed all the antigenic determinants of the intact protein. Using this common general knowledge, the skilled person would easily identify octapeptides as set forth in the pending claims.

In sum, the evidence of record plainly establishes that, following the teachings of the specification, one of skill in the art could practice the claimed invention without undue experimentation.

CONCLUSION

In view of the foregoing, Applicant submits that the claims are now in condition for allowance and requests early notification to that effect. Please direct all further communications regarding this application to:

Rebecca M. Hale
CHIRON CORPORATION
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097.

Respectfully submitted,

Date: July 12, 2004

By: _____

Dahna S. Pasternak
Attorney for Applicant
Registration No. 41,411

Chiron Corporation
Intellectual Property – R440
PO Box 8097
Emeryville, CA 94662-8097
Telephone: 650-493-3400
Facsimile: 650-493-3440